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EXAMINER: HORLICK,K

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18N1/0905

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DATE MAILED: 09/05/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 4/29/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449. (2)
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☑ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-12 are pending in the application.
   Of the above, claims - are withdrawn from consideration.
2. ☐ Claims - have been cancelled.
3. ☐ Claims - are allowed.
4. ☑ Claims 1-12 are rejected.
5. ☐ Claims - are objected to.
6. ☐ Claims - are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. The disclosure is objected to because of the following informalities: claim 8 does not end in a period; and the nucleic acid sequences on page 13 are not identified by their corresponding SEQ ID NOs. Appropriate correction is required.

16. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-5 and 7-8 are rejected under 35 U.S.C. § 103 as being unpatentable over either Burg et al. or Higuchi et al. (1993), in view of either Gershoni et al. or Krause et al.

These claims are drawn to a "system" (the claims are being treated as apparatus-type claims) comprising: an amplification reaction mixture; a sample interface comprising a fiber optic co-

axially disposed with a lens; a first fluorescent indicator capable of generating a signal proportional to the amount of an amplification product; and a second fluorescent indicator capable of generating a signal proportional to the volume of the reaction mixture.

Burg et al. teach a system comprising: an amplification reaction mixture; a sample interface comprising a fiber optic; and a fluorescent indicator capable of generating a signal proportional to the amount of an amplification product (see abstract and fig. 1). Higuchi et al. also teach a system comprising: an amplification reaction mixture; a sample interface comprising a fiber optic; and a fluorescent indicator capable of generating a signal proportional to the amount of an amplification product (see entire reference, especially the abstract and fig. 1 on page 1026). Higuchi et al. also teach normalization of fluorescence for quantitative analysis, to compensate for measurement variation, on page 1027, last paragraph, to page 1028, last full paragraph in first column. This reference suggests the use of other means of minimizing sample-to-sample fluorescence variation in the final paragraph on page 1030.

Neither of these references teach a second fluorescent indicator capable of generating a signal proportional to the volume of the reaction mixture, to be used as an internal standard.

Gershoni et al. teach measuring fluorescence of a target molecule in the presence of a second fluorescent molecule, which is used as an internal standard to account for measurement variation (see abstract and introduction on pages 315-316). Krause et al. provide the same teaching, including the use of one of the preferred dyes, fluorescein (see entire reference, especially "Materials and Methods" on page 170).

One of ordinary skill in the art would have been motivated to use a second fluorescent dye as an internal standard in the method of Burg et al. or Higuchi et al. (1993) because this would have been expected to provide more accurate quantitative measurements, as suggested by Gershoni et al. or Krause et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use the claimed "system".

17. Claims 1-5 and 7-8 are rejected under 35 U.S.C. § 103 as being unpatentable over Higuchi et al. (1992), in view of either Gershoni et al. or Krause et al.

These claims are drawn to a "system" as described supra.

Higuchi et al. teach a system comprising: an amplification reaction mixture; a sample interface comprising a fiber optic; and a fluorescent indicator capable of generating a signal proportional to the amount of an amplification product (see entire reference, especially first full paragraph and fig. 5 on page 415).

This reference does not teach a second fluorescent indicator capable of generating a signal proportional to the volume of the reaction mixture, to be used as an internal standard.

Gershoni et al. teach measuring fluorescence of a target molecule in the presence of a second fluorescent molecule, which is used as an internal standard to account for measurement variation (see abstract and introduction on pages 315-316). Krause et al. provide the same teaching, including the use of one of the preferred dyes, fluorescein (see entire reference, especially "Materials and Methods" on page 170).

One of ordinary skill in the art would have been motivated to use a second fluorescent dye as an internal standard in the

method of Higuchi et al. (1992) because this would have been expected to provide more accurate quantitative measurements, as suggested by Gershoni et al. or Krause et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use the claimed "system".

18. Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over any one of Burg et al., Higuchi et al. (1993), or Higuchi et al. (1992), in view of either Gershoni et al. or Krause et al., and further in view of Renzoni et al.

This claim is drawn to a "system" as described supra, with the added limitation of a plurality of first fluorescent indicators each corresponding to a different amplification product.

The teachings of the primary and secondary references are discussed supra.

These references do not teach the use of a plurality of first fluorescent indicators.

Renzoni et al. disclose the simultaneous detection of two or more different nucleic acids by labeling each such nucleic acid with a distinguishable fluorescent label (see column 16, line 66 to column 17, line 36).

One of ordinary skill in the art would have been motivated to use a second fluorescent dye as an internal standard in the method of any one of the primary references because this would have been expected to provide more accurate quantitative measurements, as suggested by Gershoni et al. or Krause et al. The artisan of ordinary skill would have been further motivated to use a plurality of first fluorescent indicators because this would have been expected to facilitate simultaneous detection of multiple nucleic acids, thus providing more information than only use of a single indicator (Renzoni et al.). It would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use the claimed "system".

19. Claims 1-2 and 9-11 are rejected under 35 U.S.C. § 103 as being unpatentable over Lee et al. in view of any one of Burg et al., Higuchi et al. (1993), or Higuchi et al. (1992).

These claims are drawn to the "system" as described supra, or said system with the added limitation that said amplification reaction is a polymerase chain reaction, and said first and second fluorescent indicators are covalently attached to an oligonucleotide having a nucleotide sequence complementary to a portion of a strand of said amplification product, said second indicator quenching the fluorescence of said first indicator.

Lee et al. teach a system comprising: a polymerase chain reaction amplification mixture; a first fluorescent indicator capable of generating a signal proportional to the amount of an amplification product; and a second fluorescent indicator capable of generating a signal proportional to the volume of the reaction mixture, wherein said first and second fluorescent indicators are covalently attached to an oligonucleotide having a nucleotide sequence complementary to a portion of a strand of an amplification product, said second indicator quenching the fluorescence of said first indicator (see entire reference, especially fig. 1 and "Results" on pages 3762-3763). This reference specifically suggests at the top right-hand side of page 3763 that "TMR fluorescence can be used as an internal fluorescence reference to control for pipetting errors and evaporation during thermal cycling". It is suggested in the last paragraph on page 3766 that fluorescence be detected directly in a closed reaction vessel.

Lee et al. do not teach the use of a fiber optic to detect fluorescence.

Burg et al., Higuchi et al. (1993), and Higuchi et al. (1992) each teach the use of a fiber optic to detect fluorescence in polymerase chain reaction amplification assays (see supra).

One of ordinary skill in the art would have been motivated to use a fiber optic as a detection means in the method of Lee et al. because each of the secondary references teaches the use of fiber optics for detecting fluorescence in amplification assays. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use the claimed "system".

20. Claim 12 is rejected under 35 U.S.C. § 103 as being unpatentable over Lee et al. in view of any one of Burg et al., Higuchi et al. (1993), or Higuchi et al. (1992), and further in view of Renzoni et al.

This claim is drawn to the "system" of claim 9 as described supra, with the added limitation of a plurality of first fluorescent indicators each corresponding to a different amplification product.

The teachings of Lee et al., Burg et al., Higuchi et al. (1993), and Higuchi et al. (1992) are discussed supra.

These references do not teach the use of a plurality of first fluorescent indicators.

Renzoni et al. disclose the simultaneous detection of two or more different nucleic acids by labeling each such nucleic acid with a distinguishable fluorescent label (see column 16, line 66 to column 17, line 36).

One of ordinary skill in the art would have been motivated to use a plurality of first fluorescent indicators in the system of claim 9 as rejected supra because this would have been expected to facilitate simultaneous detection of multiple nucleic acids, thus providing more information than only use of a single

indicator (Renzoni et al.). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use the claimed "system".

21. Wieder et al., cited as a reference of interest, discloses the desirability of including an internal standard to compensate for errors associated with detection drift during fluorescence measurements.

22. No claims are allowable over the prior art.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Kenneth Horlick whose telephone number is (703) 308-3905. The examiner can normally be reached on Monday-Thursday from 6:30 AM-4:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

24. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1807 is (703) 305-7939.

KENNETH R. HORLICK
PATENT EXAMINER
GROUP 1800

Kenneth R. Horlick
8/29/95